Trends in Cell Biology

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Spotlight

Asymmetric Tyrosination of Spindle Microtubules Facilitates Selfish Inheritance

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Meiotic drive is an enigmatic process that results from biased segregation of selfish genetic elements that enhance their own transmission and drive evolution. During asymmetric female meiotic divisions, selfish elements segregate preferentially towards the egg rather than polar bodies. Recent findings demonstrate that asymmetric spindle tyrosination helps selfish elements to cheat.

Sexual reproduction requires meiosis, a reductional cell division that produces haploid gametes from a diploid cell. Mendel's law of segregation states that two parental alleles of a gene segregate equally into gametes, resulting in equal distribution of each allele among the gametes. This ensures that, following fertilization, both alleles are transmitted with equal probability to progeny. However, instances of preferential transmission of certain elements, termed 'selfish elements' have been documented [1–3]. Selfish genetic elements enhance their own transmission by a process known as meiotic drive, which includes killing or disabling gametes that lack the selfish element [2,4], and preferential segregation of a particular chromosome to a specific spindle pole, which enhances its chance of being transmitted to the next generation during megasporogenesis or oogenesis, in which only one of the four nuclei resulting from meiosis persist [1,3]. In particular, female meiosis, or oogenesis, involves asymmetric division to form a large egg that persists and extrusion of a small polar body that is lost and not transmitted to the next generation. Several prerequisites for female meiotic drive have been noted: asymmetry of cell fate, meiotic spindle asymmetry, and differences between homologous chromosomes that affect their partitioning. However, the molecular mechanism of spindle asymmetry and the role of microtubules in regulating meiotic drive has been understudied.

The meiotic spindle is asymmetrically positioned close to and perpendicular to the cell cortex (Figure 1). Selfish elements tend to preferentially attach to the egg side of the spindle and hence are retained in the larger cell, the secondary oocyte, during the first meiotic division. In a recent study in *Science*, Akera *et al*. [5] examined post-translational modifications of spindle microtubules in metaphase of meiosis I (MI) and found asymmetric distribution of tyrosinated α-tubulin (Tyr α-tubulin) versus detyrosinated (dTyr) α-tubulin (Figure 1). Tyr α-tubulin was more abundant towards the cortical half, suggesting that this inequality may aid meiotic drive. Moreover, the precocious movement of the spindle from the center of the oocyte towards the cortex, by inhibition of actin polymerization, also resulted in earlier establishment of the asymmetric pattern of α-tubulin tyrosination in the spindle, with more intense tyrosination occurring in the half closer to the cortex [5]. Misoriented spindles that were aligned parallel to the cortex also displayed more tyrosination in the half of the spindle near the cortical region (not including the spindle pole), indicating that signaling from the cortex directly regulates microtubule tyrosination and is not transmitted via the spindle pole. Furthermore, cortical polarization induced by a chromatin-dependent RAN^{GTP} gradient was crucial for spindle asymmetry (Figure 1). The cortical region abutting the spindle has more actin, CDC42, and RAC GTPases. Of these, only the asymmetric localization of CDC42 was crucial for establishing spindle asymmetry. Untethering an active CDC42 mutant enhanced Tyr α-tubulin but appeared to compromise asymmetry. In contrast, localization of a constitutively active form of CDC42 to one pole of a centered spindle [6] induced asymmetry, with more Tyr α-tubulin towards the pole with active CDC42.

Variation in the cis-determinant for segregation, the centromere, may also promote female meiotic drive, as selfish centromeres would be oriented towards the pole away from the cortical side to ensure their transmission to the germline. Indeed, in hybrid mouse oocytes having homologous chromosomes distinguishable by weaker or stronger centromeres (inherited from different parents), the stronger centromeres preferentially oriented towards the spindle pole on the egg side in late metaphase of MI (Figure 1) [7]. When asymmetric α-tubulin tyrosination in the spindle was reconfigured to a symmetric distribution by expression of constitutively active RAN^{Q69L} or dominant-negative $CDC42^{T17N}$ mutants, biased orientation of strong centromeres was abolished. Furthermore, bivalents could flip their orientation in the asymmetric spindle to facilitate preferential orientation of the stronger centromeres towards the egg. The interaction of strong centromeres with more tyrosinated microtubules facing the cortical side of the spindle was unstable and prone to detachment. This bias is likely to be dependent on Tyr α-tubulin asymmetry; depletion of tubulin tyrosine ligase (TTL), that catalyzes α-tubulin tyrosination, stabilized microtubules. The propensity of stronger centromeres to form more stable attachments with detyrosinated microtubules towards the egg side of the spindle (Figure 1), that are also more stable than

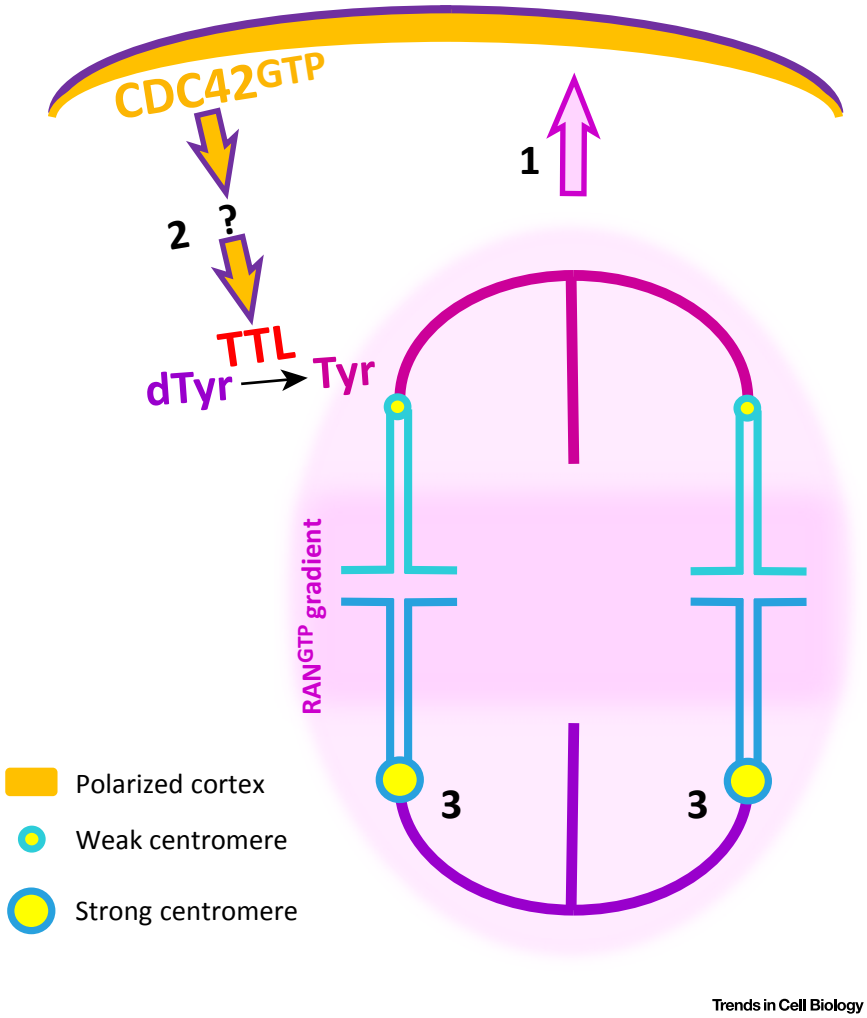

Figure 1. Model Depicting how Oocyte Spindle Asymmetry Aids Meiotic Drive. In late metaphase of meiosis II, the spindle moves closer to the cortex and is oriented perpendicular to the cortical region. Cortical polarization is achieved by a chromatin-dependent RAN^{GTP} gradient (1). $CDC42^{GTP}$ is enriched at the polarized cortex. Cortical signals dependent on regulators such as $CDC42^{GTP}$ establish spindle asymmetry by preferentially enhancing formation of tyrosinated (Tyr) α-tubulin in the cortex-proximal half of the spindle, mediated by the tubulin tyrosine ligase (TTL) via an unknown signaling mechanism (2). Tyrosination asymmetry generates differential microtubule stability in the two halves of the spindle, such that kinetochore-microtubule attachments of stronger centromeres with detyrosinated (dTyr) microtubules (purple) towards the egg side are more stable (3) but attachments to the cortical side (dark pink: tyrosinated microtubules) are unstable and tend to detach. 'Selfish' chromosomes with strong centromeres thus attain a biased orientation, facilitating their retention in the secondary oocyte after the first meiotic division and preferential transmission to the progeny, in violation of Mendel's law of segregation.

the microtubules facing the cortical side, is likely to contribute to meiotic drive.

The mechanism by which asymmetric spindle microtubule tyrosination is initiated by the cortex remains unknown. Whether signaling mediated by active cortical CDC42 preferentially activates TTL on the cortical side of the spindle, or redistributes active TTL such that there is more TTL and hence enhanced tyrosination on the cortical side, is yet to be determined. Another outstanding question is how stronger centromeres attain the biased orientation that aids their selfish inheritance. While tyrosination has been reported to destabilize microtubules [8], how the difference in abundance of α-tubulin tyrosination in the two halves of the spindle contributes to biased chromosome orientation is unclear. It is possible that the unstable attachment of strong centromeres to tyrosinated cortical microtubules results from a tyrosination-sensitive property of microtubule-associated proteins that affect microtubule dynamics and their association with other complex structures, such as kinetochores. Alternatively, centromere-associated proteins, whose abundance or activity varies on strong versus weak centromeres, may influence the stability of the tyrosinated microtubule and centromere interactions. Intriguingly, a mitotic centromere-associated kinesin (MCAK) +TIP, binds tyrosinated microtubules preferentially and triggers their disassembly [9].

Differences in the stability of interaction of strong versus weak centromeres with tyrosinated microtubules contribute to biased segregation; therefore it is also important to understand the organization of strong versus weak centromeres. Other studies, using the mouse model system to understand meiotic drive, have investigated the organization of selfish centromeres. Strong centromeres bound more kinetochore proteins (such as the microtubule binding kinetochore protein HEC1) relative to weaker centromeres [10]. Stronger centromeres also have more minor satellite repeats than weaker centromeres and have more centromere-specific nucleosomes containing the histone H3 variant CENP-A [7]. Quantification of CENP-A (that specifies the site of kinetochore assembly) and CENP-C (that binds CENP-A nucleosomes and recruits other kinetochore proteins) binding to stronger centromeres in metaphase-I

CF-1 X CHPO mouse oocytes revealed that stronger centromeres bind more CENP-A and CENP-C and orient preferentially toward the egg [7]. In addition, since the CENP-A polypeptide sequence was unaltered in strains having strong or weak centromeres, the differences in centromere DNA organization that impact kinetochore organization between strong and weak centromeres are likely to determine centromere strength.

In conclusion, these new findings establish asymmetric distribution of α-tubulin tyrosination as a molecular determinant of spindle asymmetry that is crucial for biased non-Mendelian segregation of selfish elements during female meiosis. Since preferential segregation has been observed in other instances of meiotic drive, it would be interesting to know whether a similar mechanism involving spindle asymmetry drives biased transmission of selfish elements in other organisms. In such organisms, strengthening centromeres on chromosomes with beneficial alleles, or linking alleles of genes encoding desirable traits to selfish centromeres, can facilitate their preferential transmission to progeny, enabling beneficial alleles to predominate in the population. This improved understanding of the mechanism of female meiotic drive can also be harnessed to devise strategies to favor the introduction and rapid spread of beneficial alleles in a wild population, bypassing the requirement for natural selection.

Disclaimer Statement

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